Markings to Show Changes Made," and a list of the pending claims is provided in the section entitled "Pending Claims 18-35, As Amended."

Claim Rejections- 35 U.S.C. § 112, First Paragraph

Claim 18 (and claims 19-26 and 29-35 which depend therefrom) stand rejected under 35 U.S.C. § 112, first paragraph as not being enabled by the specification. In particular, the Office Action states that while the specification is enabling for VEGF variants containing aspartic acid substitutions, the specification is not enabling for VEGF variants containing any amino acid modification, as required by the claims.

Applicant respectfully traverses.

Claim 26 requires a variant VEGF polypeptide wherein aspartic acid is substituted for cysteine. The Examiner has acknowledged that the specification provides proper guidance for an aspartic acid substitution (page 6). Accordingly, claim 26 satisfies the enablement requirement of 35 U.S.C. § 112, first paragraph, and Applicant requests withdrawal of the outstanding rejection.

The first paragraph of 35 U.S.C. §112, requires that a specification be commensurately enabling relative to the scope of the claims and the issue of enablement is thus "whether it would take undue experimentation for one ordinarily skilled in the art to produce embodiments that fall within the scope of the claims beyond any embodiment that is adequately disclosed in the specification. *Ex Parte Kung*, 17 U.S.P.Q.2d 1545, 1547 (Bd. Pat. App. & Interf. 1989) (*emphasis added*). A substantial amount of experimentation is thus permissible if it is routine or if the specification provides a "reasonable amount of guidance with respect to the direction in which experimentation should proceed." *In re Wands* 858 F.2d 731 (Fed. Cir. 1988)(*emphasis added*). *See also In re Angstadt* 190 USPQ 214, 218 (CCPA 1976) (*also discussed* in *In re Wands* 858 F.2d 731 (Fed. Cir. 1988)) standing for the

proposition that disclosure of a test with <u>every</u> species covered by a claim is not necessary for establishing enablement under 35 USC § 112, first paragraph.

Applicant has comprehensively recited and described in the specification the methods for isolating and sequencing the cDNA for wild type VEGF (*see e.g.*, page 45, lines 25-31, page 46, lines 1-25), the methods for producing VEGF variants, and the methods for chemically modifying the residues of VEGF polypeptides (*e.g.*, by covalent modification). The specification further provides that methods for generating VEGF variants include mutating VEGF wild type DNA by nucleotide site-directed mutagenesis of cysteine residues (*see e.g.*, page 15, lines 9-24, page 22, lines 6-8 and 9-31, page 23, lines 1-20, and page 41, lines 23-31 of the specification) and random mutagenesis at a particular cysteine codon to determine which substitution falls within the scope of the claims.

In particular, the amino acid modifications which may be made to VEGF are limited to substitutions at the 16 cysteine positions (*e.g.*, at residues 26, 51, 57, 60, 61, 68, 102, 104, 117, 120, 135, 137, 139, 146, 158 and 160, as shown in Figure 1) present in wild type VEGF. The skilled artisan was aware, at the time the invention was filed, that a single amino acid substitution of alanine would generally be sufficient to ascertain which of the 16 amino acid residues present in wild type VEGF could be modified to fall within the scope of the claims (*see also e.g.*, page 23, lines 3-20 and 27-29, page 41, lines 23-32 and page 42, lines 1-5). Accordingly, sixteen assays (*e.g.*, testing each of the 16 cysteine residues present in wild type VEGF) may be used to identify the specific cysteine positions in wild type VEGF which fall within the scope of the claims. One or more of the identified cysteine residues can then be replaced by one or more of a variety of amino acids (*e.g.*, other than cysteine) for producing a multiplicity of VEGF variants. The VEGF variants exhibiting the desired amino acid substitutions at the desired cysteine positions can then be tested for the required properties of inhibition of disulfide bond formation and of binding VEGF receptor without significantly

inducing a VEGF response, using the screening assays (*e.g.,* receptor binding and vascular endothelial growth assays) described in the Examples (*see e.g.,* page 44, lines 22-31, page 45, lines 1-23).

Accordingly, the methods for producing VEGF variants and for screening VEGF variants for the desired characteristics may be practiced by the skilled artisan using the procedures recited in the specification and the procedures which are known in the art. In particular, the experiments required for identifying the amino acid modifications encompassed by the claims include identification of the cysteine positions that fall within the scope of the claims (*e.g.,* using single alanine substitutions), replacing one or more of the residues at these positions with amino acids other than cysteine, and testing the VEGF variants exhibiting the desired substitutions at the desired positions using the assays provided in the Examples. Accordingly, the experiments required for identifying the amino acid modifications encompassed by the claims do not rise to the level of undue or non-routine experimentation, as suggested by the Examiner. For the foregoing reasons, Applicant respectfully requests that the Examiner withdraw the enablement rejection of claim 18 (and claims 19-26 and 29-35 which depend therefrom) under 35 U.S.C. § 112, first paragraph.

CONCLUSION

Applicant submits that the application is in form for allowance. If there are remaining issues which the Examiner believes may be resolved by telephone, she is invited to call the undersigned attorney at (415) 781-1989.

Respectfully submitted,

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VERSIONS WITH MARKINGS TO SHOW CHANGES MADE

[17.] 18. A variant vascular endothelial cell growth factor (VEGF) polypeptide which is capable of binding to a VEGF receptor without significantly inducing a VEGF response, said variant polypeptide comprising an amino acid modification of at least one cysteine residue in VEGF, wherein said amino acid modification inhibits disulfide bond formation.

[18.] 19. The variant VEGF polypeptide according to claim [17] 18 wherein said amino acid modification is a substitution of said at least one cysteine residue with a different amino acid which is incapable of participating in the formation of a disulfide bond.

[19.] 20. The variant VEGF polypeptide according to claim [18] 19 wherein said cysteine is at amino acid position 51 and/or 60.

[20.] 21. The variant VEGF polypeptide according to claim [17] 18 wherein said VEGF polypeptide is capable of inhibiting induction of a VEGF response.

[21.] 22. The variant VEGF polypeptide according to claim [20] 21 wherein said variant VEGF response is mitogenic activity.

[22.] 23. The variant VEGF polypeptide according to claim [18] 19 wherein two cysteines are substituted with a different amino acid at amino acid positions 51 and 60.

[23.] 24. The variant VEGF polypeptide according to claim [18] 19 wherein said cysteine is at amino acid position 51.

[24.] 25. The variant VEGF polypeptide according to claim [18] 19 wherein said cysteine is at amino acid position 60.

[25.] 26. The variant VEGF polypeptide according to claim [18] 19 wherein aspartic acid is substituted for cysteine.

[26.] 27. The variant VEGF polypeptide according to claim [23] 24 comprising the substitution C51D.

[27.] 28. The variant VEGF polypeptide according to claim [24] 25 comprising the substitution C60D.

[28.] 29. The variant VEGF polypeptide according to claim [17] 18 wherein said amino acid modification is a chemical modification of said at least one cysteine residue which renders said cysteine residue incapable of participating in the formation of a disulfide bond.

[29.] 30. The variant VEGF polypeptide according to claim [28] 29 wherein said chemical modification is of a cysteine residue at amino acid position 51 and/or 60 of the native VEGF amino acid sequence.

[30.] 31. An isolated nucleic acid sequence comprising a sequence that encodes the variant VEGF polypeptide of claim [17] 18.

[31.] 32. A replicable expression vector capable in a transformant host cell of expressing the nucleic acid of claim [30] 31.

[32.] 33. Host cells transformed with the vector according to claim [31] 32.

[33.] 34. Host cells according to claim [32] 33 which are Chinese hamster ovary cells.

[34.] 35. A composition of matter comprising the variant VEGF polypeptide according to claim [17] 18 in combination with a pharmaceutically acceptable carrier.